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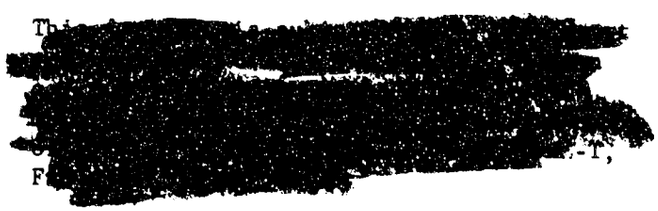

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CLEARINGHOUSE

The question of the intensity of immunity in experimental animals which recovered after treatment with streptomycin and serum.

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Zhurnal Mikrobiol., Epidemiol., i Immunobiol. 27: 1: 54-57, 1956.

The question concerning the existence of a postinfection immunity with plague is not debatable at present. At the same time the indications in the literature by Nikanorov, Belar, Veier, van Loon and many others, of re-infection by plague prove that the acquired immunity is not absolute, and that the intensity in each separate case can be different. This relativity of the post-infection immunity is determined by the individual characteristics of the macro and micro organism, by the degree of active participation of the defense forces of the organism in the process of the infection and the convalescence and by the method of the patient's therapy. The question as to the degree of intensity of the immunity which is acquired in the process of having plague in general, and the degree of dependence on the method of treating the plague patient, has a great significance and the importance of its explanation is quite evident.

The task of the present preliminary investigation was to resolve the question, can the method of treatment influence the production of the post-infection immunity, and if so, to what extent.

The determination of the intensity of immunity was conducted on infected guinea pigs, which had recovered after treatment with streptomycin (8 animals), or with a liquid, refined, concentrated gamma-globulin fraction of an anti-plague serum (12 animals).

2½ months before the re-infection, the animals were inoculated subcutaneously with a virulent plague culture (strain no. 100) in a dose equalling 2500 bacteria (which comprised 250 Dlm), and a course of treatment with streptomycin (first group - 10 g. pigs), or with the liquid refined, concentrated gamma-globulin fraction of antiplague serum (second group - 80 /typographical error; should read '30' -Translator's note/ guinea pigs). The treatment was started within 24-26 hours after infection. The streptomycin was administered over a period of 10 days, every 6 hours (4 times per 24-hour period). The streptomycin dose was calculated for 1 kg. of animal weight according to the standard system. The gamma-globulin fraction of antiplague serum was injected subcutaneously at a rate of 1 ml. over a period of 10 days (once per 24-hour period).

The results of the experiment are presented in the table, which shows that the injection of streptomycin into the animals which were infected with plague contributed to the recovery of all the guinea pigs included in the test; whereas, in the treatment with the fraction of antiplague serum, 12 guinea

pigs survived and the other 18 died with manifestations of experimentally induced plague. The control guinea pigs (third group) were not treated and all died of plague in the 6th-9th 24-hour period of the disease.

Two guinea pigs, of the group which had recovered after the streptomycin injection, a month after the start of the experiment were sacrificed, cut open and examined bacteriologically. With this, the inoculations and impressions from the organs proved to be free of the pathogen.

Two months after the completion of the treatment, the 8 guinea pigs which had recovered after the streptomycin treatment and the 12 g. pigs remaining alive after treatment with the fraction of antiplague serum were re-infected with 250 Dlm of the same strain of P. pestis . The culture was injected subcutaneously into the same inguinal region as in the first infection. A third group of animals, which had not previously been in the experiment was used as a control. An observation was conducted over a period of a month.

As is evident from the table, all of the animals which were treated earlier with streptomycin died as a result of the re-infection, with the presence of a specific pathologic-anatomical picture: an edematous subcutaneous cellular tissue; its vessels are acutely (misprint - word could be either "infected" or "injected"; Translator's note); there is at the point of the culture's injection an infiltrate the size of a pigeon egg, with a caseous decomposition in the center; the inguinal and axillary glands are enlarged, hyperemic; a mucous exudate in the thoracic cavity; in the lungs- large necrotic nodules; the lung tissue in the majority of the animals is of a dark cherry color, with areas of induration; the liver is clayey colored, the tissue fragile; the spleen is acutely enlarged, with an abundance of large and small necrotic nodules. It is necessary to note with this that the guinea pigs of this group died at somewhat later times: their average life continuance was 5 days longer than that of the control animals. Other results were received with the investigation of the intensity of immunity in the g. pigs which had been treated earlier with the liquid gamma-globulin fraction of antiplague serum: all 12 animals of this group remained alive after re-infection, whereas, the control g. pigs died within eight 24-hour periods, with manifestations typical for plague that has been experimentally induced.

Thus, the intensity of the postinfection immunity in the animals which had recovered after treatment with streptomycin and with serum is different. In those guinea pigs which had been infected with plague and treated with streptomycin, a condition of active immunity was practically not developed. Only an insignificant display of it was shown in the prolongation of life (an average of 5 days), whereas, the animals which had recovered as a result of their treatment with the fraction of antiplague serum proved to be immune to the re-inoculation with the specific culture.

The cause of the difference in the immunological condition, in all probability, should be looked for in the different mechanism of action of these preparations upon injection into the organism. In this regard, the communication of Zhirar is worthy of note: he, in his experiments, was also able to

establish that with a timely injection of streptomycin into an organism that is infected with plague bacteria, this highly active antibiotic produces such a quick and complete destruction of the plague bacteria that a condition of immunity does not have time to develop in the animals.

Analogous results of an investigation were received by Krasinskaya with a study of the influence of therapeutic preparations on the immunological reactions of animals recovering from pneumococcal infections (1950). By treating the animals, which had been infected with pneumococci, type I, with sulfadiazine (first group) and with penicillin (second group), the author established that with an early administration of penicillin, which acts bactericidally, immunity was not developed in the animals, while the use of sulfadiazine, which possesses bacteriostatic properties, does not tell negatively on the production of the immunity.

The cited data and also our own observations are in accord also with the results of the investigations of Troitskiy, Tumanyan and Dzhikidze, which attest that the injection of a therapeutic preparation can exert an influence on the production of postinfection immunity. Thus, it was established by the authors that in mice given a simultaneous injection of dysenteric bacteria (Fleksner's) and streptomycin, an immunity is formed which is significantly less intense than in the control animals.

The absence of immunity in the animals which were infected with the culture and then treated with streptomycin is apparently explained by the latter's bacteriostatic, and possibly by its bactericidal, action which stipulates such a rapid purge of the pathogen from the organism that an active immunity does not have time to develop. This is particularly true in plague, in virtue of the weak antigenic properties of the plague bacillus. In the animals treated with the serum the process of purging the infection from the organism starts at somewhat later times (from the start of the therapy); consequently, different conditions for the development of the immunity are thereby created.

While taking all these data into consideration, one should acknowledge that as a therapeutic and antibacterial agent, streptomycin is more effective than the serum. The specific serum, its refined and concentrated gamma-globulin fraction in particular, also exerts a therapeutic action. However, the mechanism of the action of each of these therapeutic preparations is different. Therefore, it would seem more perspective to consider their joint use.

It is possible that such a combination of therapeutic agents is expedient also for preventing the development of resistance to drugs in the microorganisms.

In this regard special interest is merited by the work of Smirnov-Verezhnikov, who had proposed as early as 1945-1946 a complex method of treating plague, in which sulfanilamide preparations, and also streptomycin and other antibiotics, were used in combination with the specific serum. The injection of a therapeutic serum is particularly desirable, according to the opinion of the author, in the first days of the disease when there is an absence of the necessary specific antibodies in the organism. According to the data of

Krasnoshchekovaya, in the treatment of pneumonic plague patients by the Zhukov-Verezhnikov method, one will be unable to detect a plague culture in the sputum and blood of the patients immediately after the injection of streptomycin. In the rare cases where the pathogens are detected, they appear to have a comparatively high sensitivity to streptomycin.

Under the conditions of our experimental work, where the guinea pigs were treated with streptomycin and with a gamma-globulin fraction of serum, we were also unable to isolate streptomycin-resistant strains, however, the materials we have at our disposal are definitely insufficient for a final judgement of this question. Only the necessity of making it more precise is evident.

Consequently, the task of subsequent investigations in this direction must be the study of the questions concerning the therapeutic efficacy of the combined method of administering the separate fractions of proteins by the specific serum and of antibiotics, the influence of this method on the processes of producing an active immunity in plague, and also the final explanation of the possible prevention of drug resistance in microbes by the administration of therapeutic preparations in established combinations.

Conclusions

1. In guinea pigs infected with plague and treated with streptomycin a postinfection immunity is not developed.

2. The experimental animals which had recovered through treatment with a refined, concentrated gamma-globulin fraction of antiplague serum proved to be immune to a re-inoculation with the specific culture.

3. Taking into consideration the therapeutic properties and the data concerning the different mechanism of action possessed by streptomycin and by the gamma-globulin fraction of antiplague serum, one should consider their joint use as expedient for therapeutic purposes.

Literature

Belar, Veier, van Loon - cited by N. N. Zhukov-Verezhnikov.

Zhukov-Verezhnikov, N. N. - The immunology of plague. Moscow, 1940.

Krasinskaya, S. L. - Zhurnal Mikrobiol., Epidemiol. i Immunobiol., 1951, No. 3, pp 35-40.

Troitskiy, V. L., Tumanyan, M. A., Dzhikidze, E. K. - Ibid, pp 37-43.

The results of the investigation of the intensity of immunity in guinea pigs which were inoculated with a plague culture and recovered after therapy with streptomycin and with a gamma-globulin fraction of antiplague serum.

Method and Dose of inoculation (DLm)	The designation of the preparation which was injected for therapy	Total No. of animals in a group	Number of animals which died	Number of animals which survived	Results of the re-infection of the animals which recovered: No. of animals in the group	of these: died	of these: survived	Average life continuance of the animals (in 24-hour periods)
Subcutaneously 250	Streptomycin	10	-	10	8	8	-	13.7
Subcutaneously 250	Liquid refined, concentrated gamma-globulin friction of antiplague serum	30	18	12	12	-	12	-
Subcutaneously 250	Control animals-not treated	10	10	-	10	10	-	8